Tetrahedron, 1963, Vol. 19, pp. 1527 to 1530. Pergamon Press Ltd. Printed in Northern Ireland

AN EXAMINATION OF THE PRINCIPLE OF THE ADDITIVITY OF SUBSTITUENT GROUP INFLUENCE IN BENZOIC ACIDS

J. F. J. DIPPY and S. R. C. HUGHES
Chemistry Department, Chelsea
College of Science and Technology, London

(*Received* 3 *April* 1963; *in revised form* 3 *May* 1963)

Abstract—The authors have collected the dissociation constants of poly-substituted benzoic acids in water measured by them and recorded at intervals in earlier papers. The principle of the additivity of group influences has been examined, particularly with respect to the strengths of the 34 disubstituted acid available. Deviations from the principle are discussed.

STONE and Pearson[1] have raised the question as to whether the influences of substituents on reactivity are additive. It has been stated on earlier occasions[2-4] that the evidence pointing to additivity of group influence upon multiple substitution in the benzene ring is broadly true, in the absence of steric effects, as far as our limited information discloses.

Narrowing the issue to group influences in the benzoic acid system there is no reason to suppose that the introduction of two substituents into $C_6H_5CO_2H$ will necessarily be additive. It is likely that the departure from additivity will be small in a given case, but the impact of supplementary resonance interactions, apart from steric factors, brought about by substituents X and Y in $XY{\cdot}C_6H_3{\cdot}CO_2H$ can well lead to serious departures from simple additivity. The writers and their collaborators in recent years have reported the strengths of many disubstituted and a few trisubstituted benzoic acids containing both like and unlike substituents, determined by a consistent conductimetric method of reasonable precision. As already claimed, there is evidence here for serious departure from additivity. The groups concerned have been methyl, nitro, hydroxyl, and halogeno substituents. In many cases departures are relatively small, and those <5 per cent are probably not significant, having regard to cumulative experimental error and the fact that the dissociation constant data refer to an arbitrarily chosen temperature, nevertheless the appreciable numbers of larger deviations render the results particularly interesting.

Table 2 sets out the dissociation constant data already recorded.[5] Also included are the calculated percentage departures from additivity which are expressed as

$$\frac{pK_{\text{calc.}} - pK_{\text{obs.}}}{pK_{\text{benzoic}} - pK_{\text{calc.}}} \times 100$$

---

[1] R. M. Stone and D. E. Pearson, *J. Org. Chem.* **26**, 257 (1961).

[2] H. H. Jaffé, *Chem. Rev.* **53**, 243 (1953).

[3] H. C. Brown, D. H. McDaniel and O. Haflinger in E. A. Braude and F. C. Nachod's *Determination of Organic Structures by Physical Methods* Vol. I; p. 591. Academic Press, New York (1955).

[4] J. Shorter and F. J. Stubbs, *J. Chem. Soc.* 1180 (1949).

[5] J. F. J. Dippy and S. R. C. Hughes *et al. J. Chem. Soc.* 1470 (1954); 2995 (1956); 2405 (1957); 1717 (1959).

and thus represent the deviation from the algebraic sum of the substituent effects in terms of free energy change. The values of p$K_{\text{calc.}}$ have been based on the dissociation constants measured by Dippy *et al.*[6] for monosubstituted benzoic acids (Table 1), viz.

$$\mathrm{p}K_{\text{calc.}} = \mathrm{p}K_{\mathrm{XC_6H_4CO_2H}} + \mathrm{p}K_{\mathrm{YC_6H_4CO_2H}} - \mathrm{p}K_{\mathrm{C_6H_5CO_2H}}.$$

It will be noticed from Table 2 that departures may be serious where strong supplementary resonance interaction is to be expected in view of the relative orientation and the particular mesomeric characteristics of the two substituents groups X and Y, e.g. 2-hydroxy-3-nitro-benzoic acid.

Additivity is most likely to be encountered in the 3,5-disubstituted benzoic acids since (i) mesomeric interaction between the substituents X and Y should be negligible and, (ii) steric effects will be absent. Yet in two of the cases studied so far departures are large (cf. Stone and Pearson's[1] findings with regard to 3,5-di-butyl benzoic acid).

An obvious weakness of the additivity principle is found in the fact that whereas the equation $\log K/K_0 = \rho\Sigma\sigma$ (vide Jaffe[2]) proposes that the strengths of 2,3-and 2,5-disubstituted benzoic acids should be identical, it is found in practice that they are often distinctly different, e.g. 2,5-dinitro benzoic acid is almost twice as strong as 2,3-dinitro benzoic acid. Of course there is a further steric effect at play in the 2,3-acid although it is difficult to see how it could account for this particular large disparity in strength.

Other significant features are revealed in this examination.

1. Occupation of both *ortho*-positions is expected to lead to appreciable departures because of large steric factors. This is true in six 2,6-disubstituted acids (deviations varying from −16 per cent to +64 per cent) although in the seventh case, i.e. the 2,6-dichloro acid, the departure is negligible (+3 per cent).

2. The largest relative deviation (+106 per cent) is shown by 2,3-dimethyl benzoic acid which suggests a buttressing effect by the *m*-methyl group, but this does not provide an explanation for the much smaller deviations of other 2,3-disubstituted acids some of which are in fact negative values.

TABLE 1. STRENGTHS OF MONOSUBSTITUTED BENZOIC ACIDS

Substituent	10^5K_a	pK_a
2-Methyl	12·35	3·908
3-Methyl	5·35	4·272
4-Methyl	4·24	4·373
4-tert.Butyl	3·98	4·400
2-Chloro	114	2·943
3-Chloro	14·8	3·830
4-Chloro	10·5	3·979
2-Bromo	140	2·854
3-Bromo	15·1	3·821
2-Hydroxy	101	2·996
3-Hydroxy	8·27	4·083
4-Hydroxy	2·94	4·532
2-Nitro	671	2·173
3-Nitro	32·1	3·494
4-Nitro	37·6	3·425
H-	6·27	4·203

---

[6] Collected by J. F. J. Dippy, *Chem. Rev.* **25**, 151 (1939).

TABLE 2. DEVIATIONS FROM ADDITIVITY IN THE STRENGTHS OF SUBSTITUTED BENZOIC ACIDS CONTAINING TWO (AND THREE) SUBSTITUENTS

Substituents	10^3K obs.	pK_a obs.	pK_a calc.	% deviation*
2,3-Dimethyl	0·183	3·738	3·977	+ 106
2,4-Dimethyl	0·0657	4·182	4·078	−84
2,5-Dimethyl	0·1055	3·977	3·977	nil
2,6-Dimethyl	0·568	3·246	3·614	+ 63
3,4-Dimethyl	0·0391	4·408	4·442	−14
3,5-Dimethyl	0·0500	4·301	4·341	−29
2,4,6-Trimethyl	0·366	3·437	3·584	+ 24
ditto, based on 2,6-dimethyl parent	0·366	3·437	3·416	−3
4-t-Butyl-2,6-dimethyl	0·361	3·443	3·811	+ 94
ditto, based on 2,6-dimethyl parent	0·361	3·443	3·443	nil
2,3-Dinitro	14·1	1·851	1·464	−14
2,4-Dinitro	37·6	1·425	1·395	−1
2,5-Dinitro	23·9	1·622	1·464	−6
2,6-Dinitro	72·5	1·140	0·144	−25
3,4-Dinitro	1·52	2·815	2·716	−7
3,5-Dinitro	1·50	2·824	2·784	−3
2,4,6-Trinitro	222	0·654	0·634	−27
4-Methyl-3,5-dinitro	1·07	2·971	2·954	−1
2-Chloro-3-nitro	9·51	2·022	2·234	+ 11
2-Chloro-4-nitro	10·9	1·963	2·165	+ 10
2-Chloro-5-nitro	6·80	2·168	2·234	+ 3
2-Chloro-6-nitro	45·5	1·342	0·914	−13
2-Bromo-6-nitro	42·5	1·372	0·825	−16
2,4-Dichloro	2·09	2·680	2·719	+ 3
2,5-Dichloro	3·42	2·466	2·570	+ 6
2,6-Dichloro	25·5	1·594	1·684	+ 4
2,3-Dihydroxy	1·22	2·914	2·876	- 3
2,4-Dihydroxy	0·473	3·325	3·325	nil
2,5-Dihydroxy	1·12	2·951	2·876	−6
2,6-Dihydroxy	84	1·076	1·789	+ 30
3,4-Dihydroxy	0·0323	4·491	4·412	+ 38
3,5-Dihydroxy	0·0915	4·039	3·962	−2
2-Hydroxy-3-nitro	13·4	1·873	2·287	+ 22
2-Hydroxy-4-nitro	5·88	2·231	2·218	−1
2-Hydroxy-5-nitro	7·57	2·121	2·287	+ 9
2-Hydroxy-6-nitro	5·81	2·236	0·996	−39
2-Hydroxy-3,5-dinitro	201	0·697	1·577	−34
2-Hydroxy-5-chloro	2·35	2·629	2·623	nil
2-Hydroxy-6-chloro	2·36	2·627	1·736	−36
2-Hydroxy-5-bromo	2·44	2·613	2·614	nil
2-Hydroxy-6-methyl	0·478	3·321	2·701	−41

* % deviation is calculated as (pK_{calc} − pK_{obs}) × 100/(pK_{benzoic} − pK_{calc}) to nearest 1 %.

3. It is anticipated that the remote substituent in 2,4-disubstituted acids will make no steric contribution, neither will its resonance contribution be noticeably different from that reflected in the mono-substituted acid. An inspection of Table 2 certainly

shows that in some cases the deviation is negligible, but in the case of 2,4-dimethyl benzoic acid, however, the deviation is −84 per cent and no explanation can be offered for this. The positive deviations of +24 per cent and +94 per cent found for 2,4,6-trimethyl- and 4-t-butyl-2,6-dimethylbenzoic acids respectively, when based on benzoic acid as their parent, could be attributed to inhibition of the depressing effect of *p*-alkyl when the carboxyl group is twisted out of the plane of the ring. However, calculation on the basis of the 2,6-disubstituted acid as parent in each case gives rise to negligible deviations (Table 2). Such observations serve to emphasize the complete breakdown of the additivity principle when the parent acid is sterically disturbed by the substituent group in question.

Whereas the foregoing features are among the most significant there are others than can be discerned in the comprehensive Table 2. In addition to our dissociation constant data for polysubstituted benzoic acids, there are on record the relative strengths for a limited number of such acids in non-aqueous media notably by Hetzer and Davis[7] and by Simon *et al.*[8]

The effect of two or more substituents upon other acids containing an aromatic nucleus has scarcely received any investigation. In the phenylacetic series there are only two corresponding acid strengths available,[6] and that of the 2,4-dinitro acid is noteworthy in that it departs as much as +6·4 per cent from additivity. There are no steric or mesomeric interactions here, additional to those that might be operative in the mono-substituted acids, and so one might have expected a closer conformity to the additivity relationship.

In conclusion, it must be said that the data reviewed here fail to give unequivocal support to the suggestion that the cumulative effect of substituents in the benzene ring is simply additive, in the absence of supplementary steric and mesomeric interactions. The only two systems that exclude the foregoing interactions are the 2,4- and 3,5-disubstituted benzoic acids and it is seen that many of the reported cases exhibit deviations far in excess of the significant limit.

---

[7] H. B. Hetzer and M. M. Davis, *Res. Nat. Bur. Stand.* **60,** 569 (1958).

[8] W. Simon, G. H. Lyssy, A. Mörikofer and E. Heilbronner, *Zusammenstellung von scheinbaren Dissoziationskonstanten im Lösungsmittel system Methylcellosolve-Wasser.* Juris-Verlag, Zurich (1959).